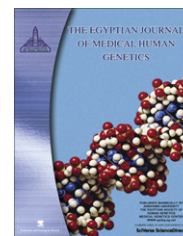




Ain Shams University

## The Egyptian Journal of Medical Human Genetics

[www.ejmhg.eg.net](http://www.ejmhg.eg.net)  
[www.sciencedirect.com](http://www.sciencedirect.com)


## REVIEW

## Hereditary periodic fever syndromes

Rabah M. Shawky <sup>a,\*</sup>, Nagwa E.A. Gaboon <sup>b</sup><sup>a</sup> *Pediatrics and Genetics Department, Ainshams University, Cairo, Egypt*<sup>b</sup> *Medical Genetics Center, Ainshams University, Cairo, Egypt*

Received 13 December 2010; accepted 28 February 2011

Available online 3 September 2011

## KEYWORDS

Periodic fever syndromes;  
 Pyrin;  
 Cryopyrin;  
 Autoinflammatory diseases;  
 Mevalonic kinase

**Abstract** Hereditary periodic fever syndromes, comprise a group of hereditary disorders with similar clinical features of recurrent short episodes of fever associated with inflammatory manifestations. These are usually self-limited in nature and occur in the absence of infection or autoimmune reaction. Between attacks, patients feel well and regain their normal daily functions until the next episode occurs. The episodes are usually associated with elevated serum levels of acute-phase reactants (e.g., fibrinogen, serum amyloid A [SAA]), an elevated erythrocyte sedimentation rate (ESR), and leukocytosis. These illnesses represent inborn errors in the regulation of innate immunity thus substantiating the distinction from autoimmune disorders, which more directly affect the adaptive immune system. Each of these disorders has a distinct genetic defect. Most of these proteins are members of the Death Domain Superfamily and are involved in inflammation and apoptosis. These proteins mediate the regulation of nuclear factor- $\kappa$ B (NF- $\kappa$ B), cell apoptosis, and interleukin 1 $\beta$  (IL-1 $\beta$ ) secretion through cross-regulated and common signaling pathways. Six periodic fever syndromes have been characterized. Genetic defects, pathogenesis, epidemiology and management of these fevers will be discussed.

© 2011 Ain Shams University. Production and hosting by Elsevier B.V. All rights reserved.

\* Corresponding author. Address: 2 Tomanbay St., Hammamat Elk obba, Cairo, Egypt. Tel./fax: +20 2 22585577.  
 E-mail addresses: [shawkyrabah@yahoo.com](mailto:shawkyrabah@yahoo.com) (R.M. Shawky), [nogao ta5000@yahoo.com](mailto:nogao ta5000@yahoo.com) (N.E.A. Gaboon).



## Contents

1.	Background	118
2.	Types	119
3.	Genetic defects and general pathogenesis	119
3.1.	Familial mediterranean fever (FMF)	119
3.1.1.	Pathogenesis	119
3.1.2.	Epidemiology	119
3.1.3.	Clinical picture	119
3.1.4.	Complications	120
3.1.5.	Diagnosis	120
3.1.6.	Management	120
3.2.	Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS)	120
3.2.1.	Pathogenesis	120
3.2.2.	Epidemiology	121
3.2.3.	Clinical picture	121
3.2.4.	Differential diagnosis	121
3.2.5.	Treatment	121
3.3.	Tumor necrosis factor receptor-associated periodic syndrome (TRAPs)	121
3.3.1.	Pathogenesis	121
3.3.2.	Epidemiology	121
3.3.3.	Clinical picture	121
3.3.4.	Diagnostic criteria [52]	121
3.3.5.	Laboratory studies	122
3.3.6.	Medications	122
3.4.	The Cryopyrinopathies	122
3.4.1.	Muckle–Wells Syndrome	122
3.4.2.	Familial Cold Autoinflammatory Syndrome (FCAS) (familial cold urticaria)	122
3.4.3.	Chronic infantile neurologic, cutaneous, articular syndrome (CINCA)	123
3.5.	Pyogenic arthritis, Pyoderma gangrenosum, and Acne (PAPA) and Blau syndromes	123
3.6.	Marshall's syndrome or PFAPA (periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis) syndrome	123
3.6.1.	Clinical picture	123
3.6.2.	Diagnostic criteria [74]	123
3.6.3.	Diagnosis	123
3.6.4.	Treatment	123
4.	Conclusion	123
	Conflict of interest	124
	References	124

## 1. Background

Hereditary periodic fever syndromes (HPFSs) are rare and distinct heritable disorders characterized by short and recurrent attacks of fever and severe localized inflammation that occur periodically or irregularly and that are not explained by usual childhood infections. These attacks undergo spontaneous remission without antibiotic, anti-inflammatory, or immunosuppressive treatment. Between attacks, patients feel well and regain their normal daily functions until the next episode occurs. The episodes are usually associated with elevated serum

levels of acute-phase reactants (e.g., fibrinogen, serum amyloid A [SAA]), an elevated erythrocyte sedimentation rate (ESR), and leukocytosis [1]. They were initially described as affecting primarily the serosal and synovial surfaces and the skin, but now recognized to include a somewhat broader distribution of affected tissues [2]. They differ from autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis in that they lack high-titer autoantibodies or antigen-specific T-cells. They are termed autoinflammatory diseases [3]. Advances in the genetics and molecular biology of the hereditary periodic fever syndromes have defined important new gene families and

**Table 1** Summarizes the gene symbols, chromosomal loci, protein products, and modes of inheritance of these diseases [1].

Syndrome	Gene and Locus	Protein	Mode of Inheritance
FMF	<i>MEFV</i> , 16P13.3	Pyrin, marenostrin	Autosomal recessive
HIDS	<i>MVK</i> , 12q24	Mevalonate kinase (MK)	Autosomal recessive
TRAPS	<i>TNFRSF1</i> , 12p13	TNF-receptor type 1	Autosomal dominant
MWS	<i>NLRP3 (CIAS1)</i> , 1q44	Cryopyrin (NALP3/ PYPAF1)	Autosomal dominant
FCAS	<i>NLRP3 (CIAS1)</i> , 1q44	Cryopyrin (NALP3/ PYPAF1)	Autosomal dominant
CINCA	<i>NLRP3 (CIAS1)</i> , 1q44	Cryopyrin (NALP3/ PYPAF1)	Autosomal dominant

pathways in the regulation of innate immunity, thus substantiating the distinction from autoimmune disorders, which more directly affect the adaptive immune system [4].

## 2. Types

Six periodic fever diseases have been well characterized over the last few years. They include familial mediterranean fever (FMF), followed by tumor necrosis factor (TNF)-receptor-associated periodic syndrome (TRAPS), and hyperimmunoglobulinemia D syndrome (HIDS). Additional syndromes include Muckle-Wells syndrome (MWS); familial cold urticaria (FCU), known also as familial cold autoinflammatory syndrome (FCAS); and chronic infantile neurological cutaneous and articular disease (CINCA), also known as neonatal onset multisystemic inflammatory disease (NOMID) [5–8], Table 1.

Another periodic fever syndrome is periodic fever, adenopathy, and pharyngitis with aphthous ulcerations (PFAPA), but it is not classified as a human autoinflammatory syndrome [9].

The differential diagnosis for periodic fever spectrum of diseases is wide and includes infectious, malignant, and autoimmune disorders, as well as factitious and iatrogenic fever. If these attacks persist for longer than 1 year and, especially if they are associated with a family history of periodic fever, the possibility of HPFS should be raised [1].

## 3. Genetic defects and general pathogenesis

Each of these disorders has a distinct genetic defect which leads to mutations in NALP proteins. Most of these proteins are members of the Death Domains Superfamily and are involved in inflammation and apoptosis. These proteins mediate the regulation of nuclear factor- $\kappa$ B (NF- $\kappa$ B), cell apoptosis, and interleukin 1 $\beta$  (IL-1 $\beta$ ) secretion through cross-regulated and common signaling pathways [9].

HPFs are Mendelian disorders associated with sequence variations in very few genes. These variations are mostly missense mutations with deleterious effects. The mutations involve NALP proteins, also known as NLRPs, belong to the CAT-ERPILLER protein family, like Toll-like receptors, involved in the recognition of microbial molecules and the subsequent activation of inflammatory and immune responses [10].

### 3.1. Familial mediterranean fever (FMF)

FMF, also known as recurrent hereditary polyserositis, [1], is the most common entity among the group of periodic fever syndromes [9].

#### 3.1.1. Pathogenesis

The gene responsible for FMF is mapped to a small interval on the short arm of chromosome 16p13.3. The FMF gene, designated MEFV (ME for Mediterranean and FV for fever). It is approximately 10 KB with 10 exons that express a 3.7-kb transcript encoding a 781 amino acid protein known as *pyrin*, or *marenostrin*, which is expressed in myeloid cells [9]; as MEFV is expressed predominantly in granulocytes, monocytes, dendritic cells, and in fibroblasts derived from skin, peritoneum, and synovium [11–13]. More than 50 mutations have been discovered, mostly of missense type. The five most common mutations (M694V, V726A, M694I, M680I, and

E148Q) are found in more than two thirds of Mediterranean patients with FMF. The most common missense mutation is M694V (substitution of methionine with valine at codon 694), which occurs in 20–67% of cases and is associated with full penetrance. Homozygosity for M694V is associated with a greater disease severity and a higher incidence of amyloidosis. The V726A mutation occurs in 7–35% of cases and is associated with milder disease and a lower incidence of amyloidosis. The E148Q mutation is associated with low penetrance and very mild phenotype. These findings suggest that phenotypic differences may reflect different mutations. As with other recessive diseases, it is likely that some heterozygous patients may show attenuated clinical symptoms, with or without increased levels of acute phase reactants [9].

#### 3.1.2. Epidemiology

FMF predominantly affects populations living in the Mediterranean region, especially North African Jews, Armenians, Turks, and Arabs. Among Armenians with FMF, the spectrum of mutations is similar to that in the non-Ashkenazi Jewish population [14]. The clinical picture of FMF in Arabs appears to be distinct, and the range and distribution of MEFV mutations are different from those noted in other ethnic groups [15].

Unlike the Jewish, Armenian, and Turkish populations, Ozturk et al. [16] did not find a single predominant mutation in Egyptian patients with FMF. The diversity of mutations among Egyptians was reported before [17] and could be related to the heterogeneous origin of the Egyptian population and the effect of different civilization marks (such as Romans, Byzantines, and Ottomans beside the original inhabitants, the Arabs) left on this country since ancient times because of its unique location at the crossroads between Africa, Europe, and Asia. In Egypt, there were five main founder mutations accounting for the vast majority of cases of FMF which were V726A, M694V, M680I, E148Q, and M694I [18]. Also R202Q and P706 might be disease-causing mutations [16].

The male-to-female ratio of cases is about 1.5–2:1, raising the possibility that the mutation has reduced penetrance in women. Many women report that attacks occur most commonly with menses and disappears during pregnancy and return after delivery. This pattern suggests that female sex hormones might influence the disease [19]. Furthermore, the risk of renal amyloidosis is higher in men than in women [20,21].

Approximately 90% of patients are younger than 20 years, and 60% of patients are younger than 10 years. Late-onset disease is usually more clinically benign than early-onset disease [1].

#### 3.1.3. Clinical picture

FMF is divided into two phenotypes, type 1 and 2:

- **FMF type 1** is characterized by recurrent short episodes of inflammation and serositis including fever, peritonitis, synovitis, pleuritis, and, rarely, pericarditis and meningitis. The symptoms vary among affected individuals, sometimes even among members of the same family. Amyloidosis, which can lead to renal failure, is the most severe complication of FMF type 1.
- **FMF type 2** is characterized by amyloidosis as the first clinical manifestation of disease in an otherwise asymptomatic individual. [22–25].

Patients with FMF have recurrent acute febrile painful attacks that last 12 h to 4 days. The pain usually involves 1–2 of the following sites at a time: abdomen 90%, chest 40%, joints 70%, muscles, scrotum 5%, and skin [1].

Abdominal attacks start with the sudden onset of fever and pain affecting the entire abdomen [26]. The febrile joint attacks, manifest as recurrent episodes of nondestructive acute monoarthritis of short duration and most frequently involve the large joints of lower extremities [27]. In about 1% of patients, it is the sole disease manifestation. Myalgia is a frequent finding in patients with familial Mediterranean fever [1]. The febrile chest attacks manifest as pleuritis. Patients have unilateral chest pain that increases on inspiration [28]. The inflammation of the tunica vaginalis testis causes a picture of acute scrotum. It usually results in self-limited, unilateral, red painful swelling of the scrotum [1]. Erysipelas-like erythema is characterized by fever and hot, tender, swollen, sharply bordered red lesions that are typically 10–35 cm<sup>2</sup> in area and occur mainly on the legs, between the ankle and the knee, or on the dorsum of the foot, that last 1–2 days. Isolated temperature elevation lasting a few hours can occur without any pain or inflammation [29].

### 3.1.4. Complications

Amyloidosis type AA amyloidosis is common in untreated individuals. It presents with persistent, heavy proteinuria leading to nephrotic syndrome and progressive nephropathy leading to end-stage renal disease (ESRD). With increased longevity of individuals with renal failure through dialysis and/or renal transplantation, amyloid deposits are being found in other organs as well [24,30]. Although this condition is mainly related to the M694V homozygous genotype, it is also reported in association with other genotypes that confer a relatively mild form of the disease. Furthermore, renal amyloidosis can occur in asymptomatic individuals who do not have attacks of serositis (phenotype II) [31].

The age of onset of FMF attacks appears to be lower in persons with amyloidosis than in those without amyloidosis. FMF-related manifestations of chest pain, arthritis, and erysipelas-like erythema are more common in those with amyloidosis. Long periods between disease onset and diagnosis are associated with a high risk of developing amyloidosis [32].

### 3.1.5. Diagnosis

The diagnostic criteria include [33]:

- Major criteria.
  - Recurrent febrile episodes of peritonitis, synovitis, or pleuritis.
  - Amyloid-associated protein (AA)-type amyloidosis with no predisposing disease.
  - Favorable response to continuous colchicine treatment.
- Minor criteria.
  - Recurrent febrile episodes.
  - Erysipelaslike erythema.
  - FMF in a first-degree relatives.

A definitive diagnosis is based on two major or one major and two minor criteria. A probable diagnosis is based on one major and one minor criteria. Most cases are currently confirmed with molecular testing [33].

**3.1.5.1. Laboratory studies.** Targeted mutation analysis and sequence analysis of selected exons [29].

During attacks, there is increased levels of acute-phase reactants (C-reactive protein, serum amyloid A, fibrinogen, haptoglobin, C3, and C4). Urinalysis demonstrates transient albuminuria and microscopic hematuria. The synovial fluid is cloudy, filled with polymorphonuclear (PMN) cells, and sterile [1].

### 3.1.6. Management

**3.1.6.1. Treatment of manifestations.** Febrile and inflammatory episodes are usually treated with nonsteroidal anti-inflammatory drugs (NSAIDs). ESRD should be treated as for other causes of renal failure. The long-term outcome of live related-donor renal transplantation in individuals with FMF-amyloidosis is similar to that in the general transplant population [34].

### 3.1.6.2. Prevention of primary manifestations.

#### • Colchicine therapy

Homozygous or compound heterozygous for the mutation Met694Val should be treated with colchicine. Colchicine is given orally for life, 1–2 mg/day in adults. Children may need 0.5–1 mg/day according to age and weight [29]. Individuals who do not have the mutation and who are only mildly affected should either be treated with colchicine or monitored every 6 months for the presence of proteinuria. Continuous treatment with colchicine appears to be less indicated for individuals who are homozygous or compound heterozygous for the mutation Glu148Gln [29].

Complications of colchicine occasionally include myopathy, toxic epidermal necrolysis-like reaction and oligospermia. Colchicine should be continued in pregnancy. Treatment with colchicine 1 mg/day prevents renal amyloidosis even if the FMF attacks do not respond to the drug.

#### • Anakinra therapy

It is an IL-1-receptor inhibitor which offers a recently safe and effective treatment (100 mg daily or every other day) for persons who do not respond to colchicine [35–41]. This drug is expensive and has mild side effects, such as painful local reactions at the site of injections and possibly bronchopulmonary infection complications. Also further studies are needed if it is to be taken continuously as required in severely affected individuals with FMF.

### 3.2. Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS)

The disorder has also been described as a variant of Still's disease [42,43] or as etiocholanolone fever [44].

#### 3.2.1. Pathogenesis

It is caused by mutations in the mevalonate kinase (MVK) gene found on chromosome 12 at 12q24. Mevalonate kinase is an enzyme that enhances the metabolism of mevalonic acid, an intermediary product of cholesterol and isoprenoid synthesis pathways. It is speculated that shortage of isoprenoid end products contributes to increased secretion of IL-1 $\beta$ , which subsequently leads to overt inflammation and fever. More than 40 different mutations of the MVK gene have been reported.

The most common mutation is V377I, likely of Dutch origin. Mutations are associated with decreased activity of mevalonate kinase in lymphocytes, leading to increased plasma levels of mevalonic acid, which is excreted in large amounts in the urine [9].

### 3.2.2. Epidemiology

This condition is reported primarily among families of European descent, especially Dutch and French [9]. The male-to-female ratio was equal in one study [45] but about 3:2 in another large series [46], which raises the possibility of reduced penetrance in women. Most patients have attacks before the end of their first year of life (median, 0.5 years). The attacks persist throughout life, although patients have a reduction in intensity and frequency of attacks after adolescence [1].

### 3.2.3. Clinical picture

Episodic attacks of fever occur every 4–8 weeks [1], last 3–7 days and are sometimes triggered by childhood immunizations. Minor trauma, surgery, and stress are known aggravating conditions [47]. Attacks manifest as high, spiking fever and is preceded by chills in 76% of patients [46]. Abdominal pain was reported in 72%, vomiting in 56%, diarrhea in 82%, and headache in 52%, polyarthralgia in 80% and a nondestructive arthritis in 68% of patients, skin lesions in 82%, and serositis in a minority of patients. Surprisingly, amyloidosis has not been recorded in any of the patients with this syndrome [1].

#### 3.2.3.1. Diagnosis. Diagnostic criteria [46,47]:

- Constant: High IgD level ( $> 100$  U/mL) measured on two occasions at least 1 month apart.
- During attacks:
  - Elevated erythrocyte sedimentation rate (ESR) and leukocytosis.
  - Abrupt onset of fever (temperature at least  $38.5^{\circ}\text{C}$ ).
  - Recurrent attacks.
  - Elevated immunoglobulin A (IgA) level.
  - Cervical lymphadenopathy.
  - Abdominal distress (vomiting, diarrhea, pain) ([67]).
  - Skin manifestations (erythematous macules and papules).
  - Arthralgias and/or arthritis.
  - Splenomegaly.
  - Measure urinary mevalonic acid (slight elevation).
  - Genetic testing to screen for the most common V377I mutation.
  - In rare cases, measure MK activity.

### 3.2.4. Differential diagnosis

Mevalonic aciduria (MVA) is typically a disease of infantile onset. It is characterized by psychomotor retardation, ataxia, failure to thrive, cataracts, and dysmorphic features [48–50]. Patients also have severe periodic fever attacks.

### 3.2.5. Treatment

Treatment is largely supportive because various standard anti-inflammatory drugs (including colchicine and steroids) fail to suppress the attacks [1]. Thalidomide resulted in a nonsignificant decrease of acute phase protein synthesis but without an effect on the attack rate [47]. A trial of simvastatin showed a

beneficial clinical effect in five of six patients [9] and a decrease in the urinary mevalonic acid concentration in all patients. No adverse effects were observed [1].

### 3.3. Tumor necrosis factor receptor-associated periodic syndrome (TRAPs)

This syndrome was previously known by other names, including (Familial Hibernian fever, Familial periodic fever, and Autosomal dominant recurrent fever [9].

#### 3.3.1. Pathogenesis

TRAPs is an autosomal dominant periodic fever. It is caused by mutation in the soluble TNF receptor superfamily 1A gene, TNFRSF1A. It is on chromosome 12 at 12p13 and encodes for type 1A TNF receptor protein. More than 40 different mutations of the gene have been reported [9]. Most mutations in TNFRSF1A mediate their effect via decreased shedding of TNFRSF1A, thereby decreasing the amount of soluble receptor available to bind soluble TNF and subsequently initiate and maintain the inflammatory response. Defective shedding only partially explains the pathophysiologic mechanism of TRAPs because some mutations have normal shedding [51]. The dramatic response for etanercept, an anti-TNF agent, suggests that TNF plays a critical role in the inflammatory process of this disease [1].

#### 3.3.2. Epidemiology

Most patients are of northern European descent. However, mutations have been reported among patients from different ethnicities, including African American, French, Belgian, Dutch, Arab, Jewish, Irish, Scottish, and many other ethnicities [52].

A male-to-female ratio of 3:2 is reported [52]. The reason that women are more protected than men is still unknown [1].

Age ranges from 2 weeks to 53 years (median 3 years). The age of onset varies within and among families.

#### 3.3.3. Clinical picture

On average, the attacks occur once every 6 weeks and last longer than 1 week. Few patients have daily pain without a clear resolution of symptoms. Abdominal and chest pain occur in 90% and 60% of patients, respectively. Arthralgia of the large joints is common, but arthritis is rare. Painful unilateral or bilateral conjunctivitis and periorbital edema are also common. In men, scrotal pain during attacks is reported, and the incidence of inguinal hernia is increased for unknown reasons. The myalgias are severely disabling and are a constant feature. Myalgias usually start the attacks and migrate centrifugally. About 84% of patients have tender, migratory erythematous patches, which typically overlie areas of myalgia and lasting for 4–21 days [53]. The prolonged attacks, conjunctivitis, and localized myalgias differentiate the TRAPs from the other syndromes of periodic fever [54,55]. Amyloidosis develops in up to 25% of the patients, depending on the specific gene mutation and duration of attacks [9].

#### 3.3.4. Diagnostic criteria [52]

- Recurrent episodes of inflammatory symptoms spanning a period longer than 6 months.



- Fever.
  - Abdominal pains.
  - Migratory myalgia.
  - Migratory erythematous patches.
  - Conjunctivitis, periorbital edema.
  - Chest pain.
  - Arthralgia or arthritis.
- Episodes last longer than 5 days on a average.
  - Responsive to glucocorticoids but not colchicines.
  - Affected family members.
  - Any ethnicity.

Patients usually report an increased severity with physical or emotional stress or after physical trauma.

### 3.3.5. Laboratory studies

Increased levels of acute-phase reactants. The immunoglobulin D (IgD) level may be elevated ( $<100$  IU/mL), and levels of soluble TNFRSF1A in the serum may be reduced during and between attacks. Polyclonal gammopathy may also be present [1].

### 3.3.6. Medications

- Etanercept (Enbrel) binds to TNF and blocks its interaction with cell-surface TNF receptors, rendering TNF biologically inactive. It modulates biologic responses that TNF induces or regulates.
- Prednisone.

## 3.4. The Cryopyrinopathies

The cryopyrinopathies are a spectrum of clinical disorders caused by mutations in CIAS1 [56–59] a nine-exon gene on chromosome 1q. Although a number of overlapping syndromes have been described, three relatively distinct clinical disorders are recognized: familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID, also known as chronic infantile neurologic cutaneous and arthropathy [CINCA] syndrome). An urticaria-like rash is common to all of the cryopyrinopathies and is characterized histologically by infiltrates of lymphocytes and neutrophils rather than mast cells, indicating that it is not true urticaria [4,60]. The onset of these syndromes occurs neonatally or during early childhood, usually as a generalized urticaria-like skin rash associated with an intense acute-phase reaction, and different inflammatory manifestations can be observed for each clinical entity [61].

The common genetic basis for these syndromes that has been observed by means of the identification of dominantly inherited mutations in the NLRP3 gene (formerly known as CIAS1, PYPAF1, or NALP3), which encodes for the cryopyrin protein, a key component of the inflammasome [57–59] support the hypothesis that the 3 CAPS diseases actually represent different points along a disease severity spectrum, where FCAS represents the mildest phenotype, MWS the intermediate one, and CINCA/NOMID the severest [60]. Supporting this hypothesis, some clinical cases of overlapping FCAS-MWS and MWS-CINCA/NOMID syndromes have been reported [62,63].

### 3.4.1. Muckle–Wells Syndrome

It is characterized by periodic episodes of non itchy skin rash, fever, joint pain, conjunctivitis, progressive hearing loss, and kidney damage [64]. Patients have recurrent “flare-ups” that arise spontaneously or be triggered by cold, heat, fatigue, or other stresses.

Hearing loss is caused by progressive nerve damage (sensorineural deafness) typically becomes apparent during the teenage years. Amyloidosis cause progressive kidney damage in about one-third of people and these deposits may also damage other organs. In addition, pigmented skin lesions may occur [65].

**3.4.1.1. Diagnosis.** History of acute febrile inflammatory attacks that last 24–72 h that result in abdominal pain, polyarthralgias, or arthritis (of large joints), myalgia, urticaria (mostly on the trunk and extremities), and conjunctivitis. Late in the course of the disease, sensorineural deafness occurs. This feature distinguishes Muckle–Wells syndrome from other inflammatory disorders. After several years, amyloidosis of the AA type develops.

**3.4.1.2. Differential Diagnosis.** It includes other HPFSs, Alport syndrome (which has the common features of renal, ear, and ocular involvement), amyloidosis, conjunctivitis, and arthritis [1].

**Laboratory testing:** mutation detection. To date, more than 90% of mutations in CAPS have been identified in exon 3 of the NLRP3 (CIAS1) gene [1].

### 3.4.1.3. Medication.

- The drug of choice for is a selective recombinant IL-1 receptor antagonist, Rilonacept. Common adverse effects include injection site reaction and upper respiratory tract infections. It may interfere with immune response to infections, and serious, life-threatening infections have been reported [1].
- Anakinra, an interleukin 1 receptor antagonist, can lead to an improvement in hearing loss [1,66].

Live vaccines should not be given concurrently [1].

### 3.4.2. Familial Cold Autoinflammatory Syndrome (FCAS) (familial cold urticaria)

**3.4.2.1. Diagnosis.** Recurrent urticarial rash is the most consistent trait occurring in all affected subjects. Additional recurrent fever and chills (93%), polyarthralgia (96%), and conjunctivitis (84%). Other commonly reported symptoms after exposure to cold include profuse sweating (78%), drowsiness (67%), headache (58%), extreme thirst (53%), nausea (51%), and myalgia [57]. Arthritis was not reported as a feature of this disease.

### 3.4.2.2. Differential Diagnosis.

- Acquired cold urticaria (ACU) is one of the most common forms of physical urticaria. The pathophysiology of ACU involves mast-cell degranulation and histamine effects. ACU typically occurs in adulthood and spontaneously resolves. It develops within minutes of direct contact with cold, resolves within hours, and can be accompanied by angioedema, wheezing, and hypotension [1].
- Other HPFS, especially MWS should be considered.

### 3.4.2.3. Laboratory studies.

- Serum IL-6 concentrations may be high.
- Numbers of mast cells and tissue histamine levels are normal [1].

### 3.4.2.4. Other tests.

- The ice cube test is performed by placing an ice cube directly on the skin for 5 min. Patients with the disease have no urticaria in response.
- Mutations detection in exon 3 of the NLRP3 (CIAS1) gene.
- **Treatment**

Recombinant IL-1 receptor antagonists (e.g., rilonacept, anakinra, and canakinumab).

### 3.4.3. Chronic infantile neurologic, cutaneous, articular syndrome (CINCA)

It is also known as neonatal-onset multisystem inflammatory disease (NOMID) [68].

**3.4.3.1. History.** It is characterized by the triad of skin rash, chronic aseptic meningitis, and arthropathy [69,70]. The typical features include a persistent and migratory urticarial rash (which is often present from birth), fever, adenopathy, hepatosplenomegaly, and a severe and deforming arthropathy (which predominantly affects the large joints). Short episodes of recurrent fevers frequently occur. The arthropathy starts early in life and has distinctive radiographic findings of premature patellar and epiphyseal long-bone ossification and resultant osseous overgrowth that leads to severe joint contractures and disability [71,72].

Progressive neurologic impairment results from chronic aseptic meningitis caused by polymorphonuclear neutrophil (PMN) infiltration. Neurologic manifestations include progressive visual defect and high-frequency hearing loss (which frequently occurs with age), cerebral ventricular dilatation, cerebral atrophy, and mental retardation.

**3.4.3.2. Physical examination.** Include fever, urticaria like skin rash, splenomegaly and lymphadenopathy, dysmorphic features (saddle-back nose, frontal bossing, and protruding eyes), short stature with short and thick extremities, macrocephaly, finger clubbing, and joint contractures (especially in the knees) without evidence of synovial thickening on palpation. Funduscopic examination may reveal papilledema and uveitis.

### 3.4.3.3. Laboratory studies.

- Serum IL-6 concentrations may be high.
- Numbers of mast cells and tissue histamine levels are normal [1]
- The ice cube test: no urticaria in response.

### 3.4.3.4. Medication.

- Treatment with colchicine, NSAIDs, and glucocorticoids may provide some relief.
- Remarkable responses to anakinra in 3 family members with MWS and 18 patients with CINCA have been reported [9].

### 3.5. Pyogenic arthritis, Pyoderma gangrenosum, and Acne (PAPA) and Blau syndromes

PAPA is an autosomal dominant disorder with mutations in the gene encoding the adaptor protein proline serine threonine

phosphatase-interacting protein (PSTPIP1) located on chromosome 15 at 15q24.

**Blau syndrome** autosomal dominant disorder that manifests with early-onset granulomatous arthritis, uveitis, rash, and flexion contractures at the fingers associated with mutations in the gene encoding CARD15 (caspase recruitment domain 15 protein), known also as NOD2 (nucleotide-binding oligomerization domain 2 protein) located on chromosome 16 at 16q12. These two syndromes are additional rare members of the hereditary periodic fever syndromes family [9].

### 3.6. Marshall's syndrome or PFAPA (periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis) syndrome

It is a pediatric periodic disease characterized by recurrent febrile episodes associated with head and neck symptoms. The origin of this syndrome, which can last for several years, is unknown. During healthy periods, patients grow normally [9].

#### 3.6.1. Clinical picture

PFAPA occurs sporadically with no ethnic predilection. Symptoms begin around 2–6 years of age and include fever, malaise, exudative appearing tonsillitis with negative throat cultures, cervical lymphadenopathy, and aphthae, and, less commonly, headache, abdominal pain, and arthralgia. The episodes last 4–6 days, regardless of antipyretic or antibiotic treatment, and occur at a frequency of 8–12 episodes/year. Findings during the episodes may include mild hepatosplenomegaly, mild leukocytosis, and elevated acute phase reactants. Both the frequency and intensity of the episodes diminish over time [9,73].

#### 3.6.2. Diagnostic criteria [74]

Regularly recurring fevers with an early age of onset (< 5 years of age).

Symptoms in the absence of upper respiratory tract infection with at least one of the following clinical signs:

- (a) aphthous stomatitis;
- (b) cervical lymphadenitis and
- (c) pharyngitis.

Exclusion of cyclic neutropenia.

Completely asymptomatic interval between episodes.

Normal growth and development.

#### 3.6.3. Diagnosis

- Cultures from the oropharynx for bacterial, fungal, and viral pathogens;
- Chest radiography and
- Laboratory studies: leukocytosis and an elevated erythrocyte sedimentation rate during febrile attacks [73].

#### 3.6.4. Treatment

Resolution of symptoms within 24 h after a single dose of prednisone (1–2 mg/kg) or bethamethasone (0.3 mg/kg). Complete resolution has also been reported after tonsillectomy. Affected children grow normally and have spontaneous resolution within 4–8 years with no long-term sequelae [9].

## 4. Conclusion

Some of these fevers are not rare and should be put in mind in deferential diagnosis of recurrent fever.

They should be differentiated from other causes of acute abdomen, arthralgia, pleuritic pain, other autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis in that they lack high-titer autoantibodies or antigen-specific T-cells.

### Conflict of interest

The authors declare that there is no conflict of interest.

### References

- [1] Shinawi M, Scaglia F. Hereditary periodic fever syndromes. [emedicine.medscape.com](http://emedicine.medscape.com).
- [2] Kastner DL, Aksentijevich I. Intermittent and periodic arthritis syndromes. In: Koopman WJ, Moreland LW, editors. *Arthritis and allied conditions*. Philadelphia: Lippincott Williams and Wilkins; 2005. p. 1411–61.
- [3] Stojanov S, Kastner DL. Familial autoinflammatory diseases: genetics, pathogenesis and treatment. *Curr Opin Rheumatol* 2005;17:586–99.
- [4] Kastner DL. Hereditary periodic fever syndromes. *Hematology* 2005;74–81.
- [5] McDermott MF, Frenkel J. Hereditary periodic fever syndromes. *Neth J Med* 2001;59(3):118–25.
- [6] McDermott MF, Aksentijevich I. The autoinflammatory syndromes. *Curr Opin Allergy Clin Immunol* 2002;2(6):511–6.
- [7] Hull KM, Shoham N, Chae JJ, Aksentijevich I, Kastner DL. The expanding spectrum of systemic autoinflammatory disorders and their rheumatic manifestations. *Curr Opin Rheumatol* 2003;15(1):61–9.
- [8] Simon A, Kremer HP, Wevers RA, et al. Mevalonate kinase deficiency: evidence for a phenotypic continuum. *Neurology* 2004;62(6):994–7, March 23.
- [9] Gedalia A. Hereditary Periodic Fever Syndromes. In: Kliegman Richard E, Behrman Hal B, Jenson Bonita F, editors. *Nelson textbook of pediatrics*, 18th ed. Saunders, Elsevier, Philadelphia. 2007;162:1029–33.
- [10] Jéru I, Duquesnoy P, Fernandes-Alnemri T, et al. Mutations in NALP12 cause hereditary periodic fever syndromes. *Proc Natl Acad Sci USA*. 2008;105(5):1614–9 [Epub 2008 Jan 29].
- [11] Centola M, Wood G, Frucht DM, et al. The gene for familial Mediterranean fever, MEFV, is expressed in early leukocyte development and is regulated in response to inflammatory mediators. *Blood* 2000;95:3223–31.
- [12] Matzner Y, Abedat S, Shapiro E, et al. Expression of the familial Mediterranean fever gene and activity of the C5a inhibitor in human primary fibroblast cultures. *Blood* 2000;96:727–31.
- [13] Diaz A, Hu C, Kastner DL, et al. Lipopolysaccharide-induced expression of multiple alternatively spliced MEFV transcripts in human synovial fibroblasts: a prominent splice isoform lacks the C-terminal domain that is highly mutated in familial Mediterranean fever. *Arthritis Rheum* 2004;50:3679–89.
- [14] Sarkisian T, Ajrapetyan H, Shahsuvaryan G. Molecular study of FMF patients in Armenia. *Curr Drug Targets Inflamm Allergy* 2005;4:113–6.
- [15] El-Shanti H, Majeed HA, El-Khateeb M. Familial mediterranean fever in Arabs. *Lancet* 2006;367:1016–24.
- [16] Ozturk A, Elbosky E, Elsayed SM, Alhodhod M, N. Akar. Mutational analysis of the MEFV gene in Egyptian patients with familial Mediterranean fever. *Turk J Med Sci* 2009;39(2):229–34.
- [17] Brik R, Shinawi M, Kepten I, Berant M, Gershoni-Baruch R. Familial Mediterranean fever: clinical and genetic characterization in a mixed pediatric population of Jewish and Arab patients. *Pediatrics* 1999;103:e70.
- [18] El-Garf A, Salah S, Iskander I, Salah H, Amin SN. *Rheumatol Int* 2009;30(10):1293–8.
- [19] Samuels J, Aksentijevich I, Torosyan Y, et al. Familial Mediterranean fever at the millennium. Clinical spectrum, ancient mutations, and a survey of 100 American referrals to the National Institutes of Health. *Medicine (Baltimore)* 1998;77(4):268–97.
- [20] Cazeneuve C, Ajrapetyan H, Papin S, et al. Identification of MEFV-independent modifying genetic factors for familial Mediterranean fever. *Am J Hum Genet* 2000;67(5):1136–43.
- [21] Gershoni-Baruch R, Brik R, Zacks N, Shinawi M, Lidar M, Livneh A. The contribution of genotypes at the MEFV and SAA1 loci to amyloidosis and disease severity in patients with familial Mediterranean fever. *Arthritis Rheum* 2003;48(4):1149–55.
- [22] Pras M. Familial Mediterranean fever: from the clinical syndrome to the cloning of the pyrin gene. *Scand J Rheumatol* 1998;27:92–7.
- [23] Langevitz P, Livneh A, Padeh S, Zaks N, Shinar Y, Zemer D, Pras E, Pras M. Familial Mediterranean fever: new aspects and prospects at the end of the millenium. *Isr Med Assoc J* 1999;1:31–6.
- [24] Shohat M, Magal N, Shohat T, Chen X, Dagan T, et al. Phenotype-genotype correlation in familial Mediterranean fever: evidence for an association between Met694Val and amyloidosis. *Eur J Hum Genet* 1999;7:287–92.
- [25] Koné Paut I, Dubuc M, Sportouch J, Minodier P, Garnier JM, Touitou I. Phenotype-genotype correlation in 91 patients with familial Mediterranean fever reveals a high frequency of cutaneous features. *Rheumatology (Oxford)* 2000;39:1275–9.
- [26] Lidar M, Kedem R, Mor A, Levartovsky D, Langevitz P, Livneh A. Arthritis as the sole episodic manifestation of familial Mediterranean fever. *J Rheumatol* 2005;32:859–62.
- [27] Brik R, Shinawi M, Kasinetz L, Gershoni-Baruch R. The musculoskeletal manifestations of familial Mediterranean fever in children genetically diagnosed with the disease. *Arthritis Rheum* 2001;44(6):1416–9.
- [28] Brik R, Gershoni-Baruch R, Shinawi M, Barak L, Bentur L. Pulmonary manifestations and function tests in children genetically diagnosed with FMF. *Pediatr Pulmonol* 2003;35(6):452–5.
- [29] Shohat M, Halpern MB. Familial Mediterranean fever. *Gene Rev* 2009. Available from: NCBI Bookshelf .[www.ncbi.nlm.nih.gov/NCBI Literature](http://www.ncbi.nlm.nih.gov/NCBI Literature).
- [30] Livneh A, Langevitz P, Shinar Y, Zaks N, Kastner DL, Pras M, Pras E. MEFV mutation analysis in patients suffering from amyloidosis of familial Mediterranean fever. *Amyloid* 1999;6:1–6 [PubMed: 10211405].
- [31] Livneh A, Langevitz P, Zemer D, et al. The changing face of familial Mediterranean fever. *Semin Arthritis Rheum* 1996;26(3):612–27.
- [32] Cefle A, Kamali S, Sayarlioglu M, Inanc M, Ocal L, Aral O, Konice M, Gul A. A comparison of clinical findings of familial Mediterranean fever patients with and without amyloidosis. *Rheumatol Int* 2005;25:442–6.
- [33] Livneh A, Langevitz P, Zemer D, et al. Criteria for the diagnosis of familial Mediterranean fever. *Arthritis Rheum* 1997;40(10):1879–85.
- [34] Sherif AM, Refaie AF, Sobh MA, Mohamed NA, Sheashaa HA, Ghoneim MA. Long-term outcome of live donor kidney transplantation for renal amyloidosis. *Am J Kidney Dis* 2003;42:370–5.
- [35] Belkhir R, Moulouguet-Doleris L, Hachulla E, Prinseau J, Baglin A, Hanslik T. Treatment of familial Mediterranean fever with anakinra. *Ann Intern Med* 2007;146:825–6.
- [36] Bhat A, Naguwa SM, Gershwin ME. Genetics and new treatment modalities for familial Mediterranean fever. *Ann N Y Acad Sci* 2007;1110:201–8.
- [37] Gattringer R, Lagler H, Gattringer KB, Knapp S, Burgmann H, Winkler S, Graninger W, Thalhammer F. Anakinra in two adolescent female patients suffering from colchicine-resistant familial Mediterranean fever: effective but risky. *Eur J Clin Invest* 2007;37:912–4.
- [38] Kuijk LM, Govers AM, Frenkel J, Hofhuis WJ. Effective treatment of a colchicine-resistant familial Mediterranean fever patient with anakinra. *Ann Rheum Dis* 2007;66:1545–6.



- [39] Calligaris L, Marchetti F, Tommasini A, Ventura A. The efficacy of anakinra in an adolescent with colchicine-resistant familial Mediterranean fever. *Eur J Pediatr* 2008;167:695–6.
- [40] Roldan R, Ruiz AM, Miranda MD, Collantes E. Anakinra: new therapeutic approach in children with familial Mediterranean fever resistant to colchicine. *Joint Bone Spine* 2008;75:504–5.
- [41] Moser C, Pohl G, Haslinger I, Knapp S, Rowczenio D, Russel T, Lachmann HJ, Lang U, Kovarik J. Successful treatment of familial Mediterranean fever with Anakinra and outcome after renal transplantation. *Nephrol Dial Transplant* 2009;24:676–8.
- [42] Prieur AM, Griscelli C. Aspect nosologique des formes systémiques d'arthrite juvénile à début très précoce: à propos de dix-sept observations. *Semin Hop* 1984;60:163–7.
- [43] Geny B, Griscelli C, Mozziconacci P. Immunoglobulin D (IgD) in childhood. II. Serum IgD levels in juvenile rheumatoid arthritis. *Biomedicine* 1974;20:125–30 [NEJM].
- [44] Driesen O, Voute PA, Vermeulen A. A description of two brothers with permanently raised non-esterified aetiocholanolone blood level. *Acta Endocrinol (Copenh)* 1968;57:177–86.
- [45] Cuisset L, Drenth JP, Simon A, et al. Molecular analysis of MVK mutations and enzymatic activity in hyper-IgD and periodic fever syndrome. *Eur J Hum Genet* 2001;9(4):260–6.
- [46] Simon A, Cuisset L, Vincent MF, et al. Molecular analysis of the mevalonate kinase gene in a cohort of patients with the hyper-igd and periodic fever syndrome: its application as a diagnostic tool. *Ann Intern Med* 2001;135(5):338–43, 4.
- [47] Drenth JP, van der Meer JW. Hereditary periodic fever. *N Engl J Med* 2001;345:1748–57.
- [48] Schafer BL, Bishop RW, Kratunis VJ, et al. Molecular cloning of human mevalonate kinase and identification of a missense mutation in the genetic disease mevalonic aciduria. *J Biol Chem* 1992;267(19):13229–38, 5.
- [49] Hoffmann GF, Charpentier C, Mayatepek E, Mancini J, Leichenring M, Gibson KM. Clinical and biochemical phenotype in 11 patients with mevalonic aciduria. *Pediatrics* 1993;91(5):915–21.
- [50] Prietsch V, Mayatepek E, Krastel H, Haas D, Zundel D, Waterham HR. Mevalonate kinase deficiency: enlarging the clinical and biochemical spectrum. *Pediatrics* 2003;111(2):258–61.
- [51] Aksentijevich I, Galon J, Soares M, Mansfield E, et al. The tumor-necrosis-factor receptor-associated periodic syndrome: new mutations in TNFRSF1A, ancestral origins, genotype-phenotype studies, and evidence for further genetic heterogeneity of periodic fevers. *Am J Hum Genet* 2001;69:301–14.
- [52] Hull KM, Drewe E, Aksentijevich I, Singh HK, Wong K, McDermott EM. The TNF receptor-associated periodic syndrome (TRAPS): emerging concepts of an autoinflammatory disorder. *Medicine (Baltimore)* 2002;81(5):349–68.
- [53] Toro JR, Aksentijevich I, Hull K, Dean J, Kastner DL. Tumor necrosis factor receptor-associated periodic syndrome: a novel syndrome with cutaneous manifestations. *Arch Dermatol* 2000;136(12):1487–94.
- [54] Joost PH, Drenth MD, Jos WM, van der Meer NMD. *Engl J Med* 2001;345:1748–57.
- [55] Dode C, Andre M, Bienvenu T, et al. The enlarging clinical, genetic, and population spectrum of tumor necrosis factor receptor-associated periodic syndrome. *Arthritis Rheum* 2002;46(8):2181–8.
- [56] Aganna E, Martinon F, Hawkins PN, et al. Association of mutations in the NALP3/CIAS1/PYPAF1 gene with a broad phenotype including recurrent fever, cold sensitivity, sensorineural deafness, and AA amyloidosis. *Arthritis Rheum* 2002;46:2445–52.
- [57] Hoffman HM, Mueller JL, Broide DH, Wanderer AA, Kolodner RD. Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle-Wells syndrome. *Nat Genet* 2001;29:301–5.
- [58] Feldmann J, Prieur AM, Quartier P, et al. Chronic infantile neurological cutaneous and articular syndrome is caused by mutations in CIAS1, a gene highly expressed in polymorphonuclear cells and chondrocytes. *Am J Hum Genet* 2002;71:198–203.
- [59] Aksentijevich I, Nowak M, Mallah M, et al. De novo CIAS1 mutations, cytokine activation, and evidence for genetic heterogeneity in patients with neonatal-onset multisystem inflammatory disease (NOMID): a new member of the expanding family of pyrin-associated autoinflammatory diseases. *Arthritis Rheum* 2002;46:3340–8.
- [60] Masters SL, Simon A, Aksentijevich I, Kastner DL. Horror autoinflammaticus: the molecular pathophysiology of autoinflammatory disease. *Annu Rev Immunol* 2009;27:621–68.
- [61] Aksentijevich I, Putnam CD, Remmers EF, Mueller JL, Le J, Kolodner RD, et al. The clinical continuum of cryopyrinopathies: novel CIAS1 mutations in North American patients and a new cryopyrin model. *Arthritis Rheum* 2007;56:1273–85.
- [62] McDermott MF, Aganna E, Hitman GA, Ogunkolade BW, Booth DR, Hawkins PN. An autosomal dominant periodic fever associated with AA amyloidosis in a North Indian family maps to distal chromosome 1q. *Arthritis Rheum* 2000;43:2034–40.
- [63] Granel B, Philip N, Serratrice J, Ene N, Grateau G, Dode C, et al. CIAS1 mutation in a patient with overlap between Muckle-Wells and chronic infantile neurological cutaneous and articular (CINCA) syndromes. *Dermatology* 2003;206:257–9.
- [64] Genetic Home Reference. Muckle-Wells syndrome; 2009. Available at: <http://ghr.nlm.nih.gov/condition=mucklewellsyndrome>.
- [65] Genetic Home Reference. Muckle-Wells syndrome; 2011. Available at: <http://ghr.nlm.nih.gov/condition=mucklewellsyndrome>.
- [66] Rynne M, MacLean C, Bybee A, McDermott MF, Emery P. Hearing improvement in a patient with variant Muckle-Wells syndrome in response to interleukin 1 receptor antagonism. *Ann Rheum Dis* 2006;65(4):533–4. Retrieved from: [http://en.wikipedia.org/wiki/Muckle-Wells\\_syndrome](http://en.wikipedia.org/wiki/Muckle-Wells_syndrome).
- [67] Hoffman HM, Wanderer AA, Broide DH. Familial cold autoinflammatory syndrome: phenotype and genotype of an autosomal dominant periodic fever. *J Allergy Clin Immunol* 2001;108(4):615–20.
- [68] Arstegui Arstegui I, Ma Dolores Lopez Saldaa, Mariona Pascal, et al. A somatic NLRP3 mutation as a cause of a sporadic case of chronic infantile neurologic, cutaneous, articular syndrome/neonatal-onset multisystem inflammatory disease. Novel Evidence of the role of low-level mosaicism as the pathophysiologic mechanism underlying mendelian inherited diseases. *Arthritis Rheumatol Am Coll Rheumatol* 2010;62(4):1158–66.
- [69] Feldmann J, Prieur AM, Quartier P, Berquin P, Certain S, Cortis E. Chronic infantile neurological cutaneous and articular syndrome is caused by mutations in CIAS1, a gene highly expressed in polymorphonuclear cells and chondrocytes. *Am J Hum Genet* 2002;71(1):198–203.
- [70] Prieur AM. A recently recognised chronic inflammatory disease of early onset characterised by the triad of rash, central nervous system involvement and arthropathy. *Clin Exp Rheumatol* 2001;19(1):103–6.
- [71] Torbiak RP, Dent PB, Cockshott WP. NOMID – a neonatal syndrome of multisystem inflammation. *Skeletal Radiol* 1989;18(5):359–64.
- [72] Khemani C, Khubchandani R. Cinc syndrome, Indian. *Indian Pediatr* 2007;4:933–6.
- [73] Berlucchi M, Nicolai P. Marshall's syndrome or PFAPA (periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis) syndrome. *Orphanet Encyclopedia* 2004.
- [74] Thomas KT, Feder HM, Lawton AR, Edwards KM. Periodic fever syndrome in children. *J Pediatr* 1999;135:15–21.